Mitochondrial alterations by PARKIN in dopaminergic neurons using PARK2 patient-specific and PARK2 knockout isogenic iPSC lines.

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Public Summary:
In this study, we used patient-specific and isogenic PARK2-induced pluripotent stem cells (iPSCs) to show that mutations in PARK2 alter neuronal proliferation. The percentage of TH(+) neurons was decreased in Parkinson's disease (PD) patient-derived neurons carrying various mutations in PARK2 compared with an age-matched control subject. This reduction was accompanied by alterations in mitochondrial:cell volume fraction (mitochondrial volume fraction). The same phenotype was confirmed in isogenic PARK2 null lines. The mitochondrial phenotype was also seen in non-midbrain neurons differentiated from the PARK2 null line, as was the functional phenotype of reduced proliferation in culture. Whole genome expression profiling at various stages of differentiation confirmed the mitochondrial phenotype and identified pathways altered by PARK2 dysfunction that include PD-related genes. Our results are consistent with current model of PARK2 function where damaged mitochondria are targeted for degradation via a PARK2/PINK1-mediated mechanism.

Scientific Abstract:
In this study, we used patient-specific and isogenic PARK2-induced pluripotent stem cells (iPSCs) to show that mutations in PARK2 alter neuronal proliferation. The percentage of TH(+) neurons was decreased in Parkinson's disease (PD) patient-derived neurons carrying various mutations in PARK2 compared with an age-matched control subject. This reduction was accompanied by alterations in mitochondrial:cell volume fraction (mitochondrial volume fraction). The same phenotype was confirmed in isogenic PARK2 null lines. The mitochondrial phenotype was also seen in non-midbrain neurons differentiated from the PARK2 null line, as was the functional phenotype of reduced proliferation in culture. Whole genome expression profiling at various stages of differentiation confirmed the mitochondrial phenotype and identified pathways altered by PARK2 dysfunction that include PD-related genes. Our results are consistent with current model of PARK2 function where damaged mitochondria are targeted for degradation via a PARK2/PINK1-mediated mechanism.